IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No. : 4,650,787
Patentee : Schally et al.
Issue Date : March 17, 1987
Serial No. : 06/727,105
Filed : April 25, 1985
Title : BIOLOGICALLY ACTIVE OCTAPEPTIDES

Attorney Docket No. 16947-005001

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPLICATION FOR INTERIM EXTENSION OF PATENT TERM

Please find enclosed:

1. Application for Fourth Interim Extension of Patent Term (9 Pages);
2. Exhibit J – (1 Cover page, 2 pages of Exhibit);
3. Check of $220 in payment of the fee (37 C.F.R. § 1.20(j)(3)).

Please apply all other charges to Deposit Account 06-1050.

Respectfully submitted,

24 March 2008

ANITA L. MEIKLEJOHN
Reg. No. 35,283

Fish & Richardson PC
225 Franklin St.
Boston MA 02110

Enclosure: Exhibit J

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CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EV 828214087 US

March 24, 2008
Date of Deposit

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APPLICATION FOR FOURTH INTERIM EXTENSION OF PATENT TERM UNDER 35 U.S.C § 156(d)(5)

I. Pursuant to 35 U.S.C. § 156(d)(5), Debiovision Inc. ("Debiovision"), a corporation incorporated under the laws of Quebec, Canada, with its registered office at 666 Sherbrooke Street West, Suite 1400, Montreal, Quebec H3A 1E7, Canada, hereby applies for a fourth one-year interim extension of patent term for United States Patent No. 4,650,787 ("the '787 patent").[1] The '787 patent covers Sanvar™ Injection ("Sanvar") and methods of using Sanvar.[2] Debiovision is the current name of H3 Pharma, Inc. ("H3 Pharma"), the named applicant of the first Application for Interim Extension of Patent Term for this patent, filed April 9, 2005 ("First IE Application"). The certification of this name change ("Certificat De Modification") by Registraire des enterprise Québec on September 1, 2005 was provided as Exhibit A in the Application for Second Interim Extension of Patent Term for this patent, filed March 23, 2006 ("Second IE Application").

[1] A copy of the '787 patent has been provided as Exhibit 1of the Application for Interim Extension of Patent Term for this patent, filed April 9, 2005. All exhibits identified by numbers herein refer to the exhibits filed in the Application for Interim Extension of Patent Term for this patent, filed April 9, 2005. All exhibits identified by capitalized letters herein refer to the exhibits filed in either the Application for Second Interim Extension of Patent Term for this patent, filed March 23, 2006 (Exhibits A-H) or the Application for Third Interim Extension of Patent Term for this patent, filed March 23, 2007 (Exhibit I).

[2] Sanvar is also known by the trade name Octastatin™.

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II. Debiovision certifies that it is the exclusive agent for Debiopharm S.A. and Debio Recherche Pharmaceutique S.A. (collectively "Debio") for the purposes of pursuing a patent term extension for the '787 patent, by virtue of the Authorization for Debiovision to Apply for Extension of Patent Term (Exhibit B of the Second IE Application) and the Authorization for H3 Pharma to Apply for Extension of Patent Term (Exhibit 2 of the First IE Application). In the Authorizations, Debio appoints Debiovision as its sole agent for the purposes of pursing interim and permanent patent term extensions for the '787 patent. Also, in the Authorizations, Debio certifies that Debio is the exclusive licensee of the '787 patent, by virtue of a license received from The Administrators of The Tulane Educational Fund ("Tulane"), the assignee of 100% of the right, title and interest in the '787 patent (see Exhibit 3 of the First IE Application), and that Tulane has exclusively granted all patent rights in the '787 patent to Debio, including the right to pursue patent term extensions. Debio has granted Debiovision a sublicense to the '787 patent, including the rights to develop and commercialize vapreotide acetate, the active ingredient in Sanvar.

III. Debiovision has previously provided information required by 37 C.F.R. §§ 1.740 and 1.741 in the First IE Application. Additional information is provided below with reference to the relevant part of the First IE Application:

1. The complete identification of the product currently undergoing regulatory review is Sanvar™ Injection. The active ingredient of Sanvar is vapreotide acetate, an acetate salt of vapreotide, which is a synthetic analogue of somatostatin. Vapreotide is an octapeptide having the following chemical formula:

D-Phe – Cys – Tyr – D-Trp – Lys – Val – Cys – Trp-NH_2

The line between the Cys residues indicates a disulfide linkage. The structural formula of vapreotide is shown in Exhibit 4 of the First IE Application.

Sanvar is manufactured according to the description in Drug Master File No. 17133 submitted to the Food and Drug Administration by Genzyme Pharmaceuticals on December 31, 2003. Briefly, vapreotide is synthesized by coupling peptide fragments according to the sequence indicated above, using optically pure peptides and standard segment condensation protocols, in which α-amino and α-carboxyl groups and lateral side chains are protected as necessary. The octapeptide is formed by azide coupling of the two tetrapeptide fragments (synthesized in solution). The disulphide bridge is formed by iodine oxidation. The protected octapeptide disulphide is purified by chromatography and then deprotected by treatment with formic acid. The product is purified by reverse phase HPLC chromatography and vapreotide acetate is formed by ion exchange of vapreotide and TFA. The steps for synthesis of vapreotide acetate are outlined in Exhibit 5 of the First IE Application.

Sanvar is provided in single dose vials containing a sterile, lyophilized powder containing 0.6 mg vapreotide acetate (peptide base units) to be reconstituted to 50 mL with 0.9% Sodium Chloride Injection, USP, prior to infusion. The 0.9% Sodium Chloride Injection, USP, is not provided with Sanvar and does constitute part of the new drug application that is the basis for this application. Each vial of Sanvar contains a 10% overfill of vapreotide acetate to allow for losses during extraction and administration.

Sanvar reproduces most of the effects induced by natural somatostatin. In the pituitary gland, Sanvar inhibits the secretion of growth hormone. In the gastrointestinal tract, Sanvar inhibits the secretion of many endocrine digestive peptides, e.g., insulin, glucagon, gastrin, vasoactive intestinal peptide, secretin, and cholecystokinin. Sanvar also suppresses exocrine secretion from the pancreas and gastrointestinal tract. In the new drug application that is the basis for this application, Sanvar is indicated for the treatment of esophageal variceal hemorrhage in patients with portal hypertension.

2. Under section 505(b) of the Federal Food, Drug and Cosmetic Act, regulatory review is ongoing for new drug application (NDA) number 21-761 for Sanvar. This NDA was initially submitted on February 27, 2004 and is still under review.

3. Applicant reasonably expects that the regulatory review period for the new drug application will extend beyond the expiration of the term of the '787 patent, i.e., April 25, 2008, as extended by the Order Granting Interim Extension dated April 3, 2007. An approvability letter for Sanvar was mailed on December 21, 2004 and is of record in the First IE Application as Exhibit 7.

4. Vapreotide acetate, the active ingredient in Sanvar, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

5. Pursuant to 35 U.S.C § 156(d)(5)(C) and 37 C.F.R. § 1.790(a), this application is being timely submitted during the period beginning 60 days before and ending 30 days before the expiration of the preceding interim extension on April 25, 2008.

6. The U.S. Patent for which an extension is being sought is United States Patent No. 4,650,787. The names of the inventors are Andrew V. Schally and Ren Z. Cai. The '787 patent was filed on April 25, 1985, issued on March 17, 1987, and will expire on April 25, 2008 pursuant to the Order Granting Interim Extension dated April 3, 2007.

7. A copy of the '787 patent is available as Exhibit 1 of the First IE Application.

8. A copy of a Maintenance Fee Statement for the '787 patent, dated February 12, 2004 is available as Exhibit 6 of the First IE Application. The Maintenance Fee Statement shows that the maintenance fees for the fourth, eighth, and twelfth years were paid on September 10, 1990, June 17, 1994, and August 17, 1998, respectively. Applicant certifies that no disclaimer, certificate of correction, or re-examination certificate related to the '787 patent has been issued.

9. As described below, claims 1, 3, 4, 6, and 14 of the '787 patent read on the product Sanvar.

Claims of '787 Patent	How Claim Reads on Sanvar
1. A compound of the formula A – C" – X – Z – Lys – Y – C' – B wherein A is an L, D or DL amino acid selected from the group consisting of phenylalanine (Phe), its acetylated derivatives or a pharmaceutically acceptable acid addition salt thereof; B is an L, D or DL amino acid selected from the group consisting of threonine amid (Thr NH_2), tyrosine amide (Tyr NH_2), tryptophan amide (Trp NH_2); X is L-phenylalanine (L-Phe) or L-tyrosine (L-Tyr); Y is L-valine (L-Val); Z is D-tryptophan (D-Trp); and C" and C' are L or D-cysteine (Cys), -aminobutyric acid (Abu), aspartic acid (Asp) or lysine (Lys); provided that where C' is Cys, C" is also Cys and where C' or C" are other than Cys, C" is different from C' and is other than Cys; the connecting line between C" and C' signifies a bridge selected from the group consisting of carbon/carbon, carbon/sulfur, sulfur/sulfur and amide bridges; and the pharmaceutically acceptable acid addition salts thereof.	Vapreotide, the active ingredient of Sanvar, is a compound of the formula: D-Phe – Cys – Tyr – D-Trp – Lys – Val – Cys – Trp-NH_2 wherein the line connecting the two Cys residues indicates a sulfur/sulfur bridge.
3. A compound according to claim 1 wherein C" is Cys; X is Tyr; Z is D-Trp; Y is Val; and C' is Cys.	Claim 3 reads on vapreotide, as described above with respect to claim 1.
4. A compound according to claim 1 wherein C" is Cys; X is Tyr; Y is Val; and C' is Cys.	Claim 4 reads on vapreotide, as described above with respect to claim 1.

Claims of '787 Patent	How Claim Reads on Sanvar
6. A compound according to claim 1 which is – D-Phe – Cys – Tyr – D-Trp – Lys – Val – Cys – Trp-NH_2	Claim 6 reads on vapreotide, as described above with respect to claim 1.
14. A pharmaceutical composition effective for reducing growth hormone serum levels which comprises an octapeptide of claim 1, its reduced form or a pharmaceutically acceptable acid addition salt thereof in a pharmaceutically acceptable liquid or solid carrier thereof.	Sanvar is effective for reducing growth hormone levels. Sanvar contains a sterile, lyophilized powder containing 0.6 mg vapreotide acetate, which is an octapeptide covered by claim 1, as described above. The powder is contained in a single dose vial to be reconstituted with 0.9% sodium chloride injection, USP, a pharmaceutically acceptable liquid carrier.

As described below, claim 16 of the '787 patent reads on a method of using Sanvar for the treatment of esophageal variceal hemorrhage in patients with portal hypertension, which is the indication set forth in the NDA.

Claims of '787 Patent	How Claim Reads on Method of Using Sanvar
16. A method of treating excess release of growth hormone, gastrointestinal disorders, and diabetes in a mammal in need of such therapy which comprises administering to said mammal an effective dose of octapeptide of claim 1, its reduced form, or a pharmaceutically acceptable acid addition salt thereof.	Sanvar is indicated for the treatment of esophageal variceal hemorrhage in patients with portal hypertension, which is a gastrointestinal disorder.

10. The relevant dates and information required pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

Investigational new drug (IND) application number 59,287, which covers Phase III testing of vapreotide acetate (i.e., Sanvar) for the treatment of bleeding due to pancreatic resection, was received by FDA on November 23, 1999. FDA acknowledged receipt of this application on December 1, 1999. FDA completed a Phase III protocol review for a study on bleeding during pancreatic resection on April 11, 2000. Further information is available in Exhibit 8 of the First IE Application, Exhibit D of the Second IE Application and Exhibit I of the Application for Second Interim Extension of Patent Term for this patent, filed March 23, 2006 ("Third IE Application").

New drug application (NDA) application number 21-761 for Sanvar, for the treatment of variceal hemorrhage due to portal hypertension associated with therapeutic endoscopy, was initially submitted to the Food and Drug Administration (FDA) on February 27, 2004.

A copy of the approvability letter for Sanvar is available as Exhibit 7 of the First IE Application.

11. Attached as Exhibit J is a brief description of the significant activities undertaken by Debiovision with respect to Sanvar since February 28, 2007. Activities on or prior to January 11, 2005 are described in Exhibit 8 of the First IE Application; activities between January 11, 2005 and March 7, 2006 are described in Exhibit D of the Second IE Application. Activities between March 6, 2006 and February 12, 2007 are described in Exhibit I of the Third IE Application. J. Kay Noel and Associates refers to Debiovision's regulatory agent in the United States. Further information is available upon request.

12. The length of the interim extension requested is one year, pursuant to 35 U.S.C. § 156(d)(5)(B), to thereby extend the term of the '787 patent to April 25, 2009. The '787 patent is eligible for the interim extension herein applied for because it satisfies all of the requirements for such interim extension as follows:

35 U.S.C. § 156(a)

The '787 patent claims the product Sanvar and a method of using Sanvar.

35 U.S.C. § 156(a)(1)

The term of the '787 patent has not expired before submission of this application.

35 U.S.C. § 156(a)(2)

The term of the '787 patent has never been extended under 35 U.S.C. § 156(e)(1).

35 U.S.C. § 156(a)(3)

The application for interim extension is submitted by Debiovision, as the agent of Debio, which is the agent of Tulane, the owner of record, as discussed above.

35 U.S.C. § 156(a)(4)

The product, Sanvar, is subject to a regulatory review period before it can be commercially marketed or used.

35 U.S.C. § 156(a)(5)(A)

The commercial marketing of the product, Sanvar, after the regulatory review period indicated herein, will be the first permitted commercial marketing of the product under section 505(b) of the Federal Food, Drug and Cosmetic Act, under which such regulatory review is occurring.

13. Debiovision acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought by this application.

IV. By the power of attorney provided as Exhibit C of the Second IE Application, Debiovision appointed Anita L. Meiklejohn, Ph.D., Reg. No. 35,283, and Ramon K. Tabtiang, Reg. No. 55,658, of Fish & Richardson P.C., as its attorneys to prosecute its application(s) for patent term extension of U.S. Patent No. 4,650,787 and to transact all business in the Patent and Trademark Office connected therewith with full powers of substitution and revocation.

V. Please direct all communications regarding the application to

Anita L. Meiklejohn
FISH & RICHARDSON P.C.
225 Franklin St.
Boston MA 02110
Telephone: (617) 521-7041
Facsimile: (617) 542-8906

This correspondence address updates and supersedes the address provided in the Power of Attorney.

VI. It is respectfully requested, under 35 U.S.C. § 156(d)(5) and 37 C.F.R. § 1.790, that this application for interim extension of the patent term of United States Patent No. 4,650,787 be granted.

VII. The prescribed fee of $220.00 for receiving and acting upon the application for subsequent extension, pursuant to 37 C.F.R. § 1.20(j)(3), is enclosed. Please apply all other charges or credits to Deposit Account 06-1050.

Respectfully submitted,

24 March 2008

ANITA L. MEIKLEJOHN
Reg. No. 35,283

Fish & Richardson PC
225 Franklin St.
Boston MA 02110

Enclosures: Exhibit J